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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|-------------|----------------------|---------------------|------------------|
| 10/630,968 | 07/31/2003 | John J. Rossi | 1954-401 | 3645 |
| 6449 | 7590 | 03/17/2009 | EXAMINER | |
| ROTHWELL, FIGG, ERNST & MANBECK, P.C. 1425 K STREET, N.W. SUITE 800 WASHINGTON, DC 20005 | | | SHIN, DANA H | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1635 | |
| | | | NOTIFICATION DATE | DELIVERY MODE |
| | | | 03/17/2009 | ELECTRONIC |

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

| | | |
|---|------------------------|---------------------|
| Advisory Action Before the Filing of an Appeal Brief | Application No. | Applicant(s) |
| | 10/630,968 | ROSSI ET AL. |
| | Examiner | Art Unit |
| | DANA SHIN | 1635 |

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 12 February 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) The period for reply expires 3 months from the mailing date of the final rejection.
- b) The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
- (a) They raise new issues that would require further consideration and/or search (see NOTE below);
 - (b) They raise the issue of new matter (see NOTE below);
 - (c) They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
 - (d) They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. Applicant's reply has overcome the following rejection(s): _____.
6. Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. For purposes of appeal, the proposed amendment(s): a) will not be entered, or b) will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: 1-9, 17, 19-23 and 30-32.

Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See Continuation Sheet.
12. Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. Other: _____.

/J. E. Angell/
Primary Examiner, Art Unit 1635

Continuation of 11. does NOT place the application in condition for allowance because: Applicant's arguments filed on February 12, 2009 pertaining to claims 1-9, 17, and 19-23 are fully considered but they are not persuasive. Applicant argues that the claimed PCR-based amplification method of producing a mammalian promoter-containing siRNA expression cassette is unobvious because neither Engelke et al. nor Livache et al. taught the structure of the two oligonucleotide primers claimed in the instant case. It is true that the claimed oligonucleotide primers per se are not taught by either Engelke et al. or Livache et al. Nevertheless, it was common sense in the art that oligonucleotide primers are used to synthesize a desired target sequence by "acting as a point of initiation of synthesis when placed under conditions in which synthesis of a primer extension product which is complementary to a nucleic acid strand induced", wherein the oligonucleotide primers are used in PCR-based amplification methods. See paragraphs 0070 and 0073 of Engelke et al. With regard to amplifying a promoter sequence, Livache et al. teach using a PCR-based amplification method comprising primers complementary to the 5' promoter sequence, when each strand or the RNA duplex to be transcribed is flanked by two promoters. See column 2, lines 65-67; column 3, lines 1-5; lines 56-59. Hence, Livache et al. suggested that each oligonucleotide primer comprise a complementary sequence to the 5' end or a 3' end promoter sequence when a single promoter sequence, instead of two promoters, is to be used for transcribing an RNA duplex. Thus, combining the teachings of the two prior art references, one of ordinary skill in the art would have reasonably determined necessary PCR reaction reagents for producing a U6 promoter-containing double-stranded siRNA expression cassette: 1) an oligonucleotide primer comprising a complementary sequence to the 5' end of the mammalian U6 promoter sequence; 2) an oligonucleotide primer comprising a complementary sequence to the 3' end of the U6 promoter, further comprising a complementary sequence to one of the strands of the siRNA duplex because the two strands of the siRNA duplex to be transcribed is operably linked to 3' end of the U6 promoter sequence.

Applicant further argues that Livache et al. teach away from using the primers claimed in the instant case. However, applicant has failed to provide sufficient reasons or further elaborate on why the teachings of Livache et al. would have prevented one of ordinary skill in the art from making and using the claimed primers.

Applicant further asserts that there is no motivation to combine the teachings of Engelke et al. and Livache et al., because the problems associated with naked siRNAs were solved by the expression cassettes of Engelke et al. Contrary to applicant's assertion, any one of ordinary person in the pertinent art would agree that PCR method of producing a desired nucleic acid construct is less laborious and more rapid, and probably less costly than the restriction enzyme-based cutting, ligating, and cloning steps necessary to make the nucleic acid construct of Engelke et al.

Since the structure of an expression cassette comprising a mammalian promoter (e.g., U6) operably linked to a double-stranded siRNA sequence was known in the art (see for example Figure 4 and paragraph 0014 of Engelke et al.) and the practical utility of the siRNA expression cassette for long-term expression siRNAs in an animal cell with reduced expenses was known in the art as taught by Engelke et al. (see the entire reference), and PCR-amplification method for synthesizing expression cassettes was known to be more rapid compared to the restriction-enzyme-based cloning method of Engelke et al., and since the method of PCR-based synthesis/amplification of a promoter-containing target sequence was known in the art as taught by Livache et al. in addition to the general common sense pertaining to the use of oligonucleotide primers, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

With regard to claims 30-32, applicant argues that neither Noonberg et al. nor Dietz discloses PCR amplification of the claimed promoter sequence and therefore neither of them cures the deficiencies of the combined teachings of Engelke et al. and Livache et al. Contrary to applicant's argument, the combined teachings of Engelke et al. and Livache et al. provide sufficient guidelines, motivation, and expectation of success in arriving at the PCR amplification of the claimed oligonucleotide primers for the reasons stated above. Hence, this rejection is maintained.